REMARKS

Claims 49-64 were pending. The Office rejected claims 49-64. Applicants have herein amended claims 49-63; cancelled claim 64; and added new claims 65-74. Support for the amendments and new claims can be found throughout the specification and the original claims; *see, e.g.*, paragraphs [0124] – [0125]; [0203] ("the fibrin binding polypeptides . . . may be conformationally restrained by disulfide linkages between the two cysteine residues in their sequence"); [0203] (generally stating that both disulfide-linked and linear versions of the polypeptides are disclosed); [0217]; [0226-0237] (generally directed to methods and agents for Magnetic Resonance Imaging); and Examples 11- 14 (generally directed to preparation of MR imaging agents and evaluation of binding affinities of the same to fibrin and blood clots) of U.S. Publ. No. 2005/0261472 A1, the U.S. patent publication of the pending application. No new matter has been added. Accordingly, claims 49-63 and 65-74 are pending.

Applicants provide herein an updated Sequence Listing, in computer-readable and paper form, for the Office's review and consideration. The Sequence Listing provides the new sequences and sequence identifiers as indicated in the pending claims.

In light of the amendments and the remarks herein, Applicants respectfully request reconsideration and allowance of the pending claims.

Procedural History and Background

Applicants note the Examiner's outline of the Procedural History of the parent case, U.S. Ser. No. 09/627,806, in the Office Action at pages 2-3. In particular, the Examiner asserted that the various polypeptides of the present application's unamended claims were *identical* to the various polypeptides as claimed in the parent case because the sequences employed the same sequence identifiers (*see, e.g.*, page 2 of the Office Action, end of the second full paragraph; and page 3 of the Office Action, paragraph above the § 112 rejection). Applicants also note that the Examiner concluded at page 4 of the Office Action that the sequence identifiers in the parent case were deemed to identify *linear* sequences, as description was not given to the parent sequence identifiers per MPEP § 2401 to identify them as cyclic.

In order to clarify some of the amendments and remarks herein, and to refresh the Examiner's memory, Applicants again refer the Examiner to the prosecution history of the parent case, U.S. Ser. No. 09/627,806. In particular, Applicants refer the Examiner to the many communications between Applicants' former counsel and the (prior) Examiner, including the Restriction Requirement dated September 27, 2001, the Petition under 37 C.F.R. § 1.181 regarding the Restriction Requirement received June 21, 2002, the Decision on Petition dated September 13, 2002, and the Interviews dated April 2, 2003, April 3, 2003, and April 8, 2003, regarding the Decision on Petition.

Upon reviewing the Procedural History in the parent case, and in an effort to advance prosecution, but without expressing acquiescence or agreement with any of the statements, alleged admissions, or conclusions drawn in the Restriction Requirement, the Petition, or the Decision on Petition, Applicants' current counsel has amended the present claims to recite MR imaging agents. The MR imaging agents include a polypeptide comprising a disulfide-linked peptide having an amino acid sequence as set forth in the claims. Applicants respectfully point out that the amended and new claims set forth *new* sequence identifiers for the disulfide-linked peptides recited therein, with the appropriate description in the updated sequence listing identifying them as such. Thus, the claims recite disulfide-linked, rather than linear, peptides. As amended, the recited polypeptides are conjugated, optionally through a linker, to a paramagnetic metal MR chelate. Finally, the MR imaging agents are capable of binding fibrin.

Applicants respectfully assert that the recited disulfide-linked peptides are not identical to the various polypeptides that were at issue in the Restriction Requirement, Petition, and Decision on Petition. In addition, Applicants respectfully assert that any of the conclusions or alleged admissions set forth in the Restriction Requirement, the Petition, and the Decision on Petition are not applicable to the present claims. In support, Applicants respectfully note that the Examiner stated in the present Office Action that the various polypeptides of the (unamended) present claims were "identical to the various polypeptides claimed, that were at issue in the petition, in the parent application . . . *because both sets of polypeptides have the same sequence identifiers* (emphasis added)" and that the previous sequence identifiers were "deemed to" identify linear

peptides. Because the claims now recite disulfide-linked peptides, with new sequence identifiers and descriptions of the disulfide linkages in the sequence listing, the presently recited polypeptides are not identical to and were not at issue in the petition in the parent case. Moreover, Applicants note that in the Interview Summary dated April 3, 2003, the (prior) Examiner stated, in response to prior counsel's question regarding allowability of cyclic peptides, that "cyclic peptides were not part of the initial restriction, and have not been examined." Given all of the above, Applicants respectfully assert that the statements, alleged admissions, and/or conclusions set forth in the parent case's Restriction Requirement, Petition, and Decision on Petition, are therefore not applicable to the presently amended claims.

Rejections under 35 U.S.C. § 112, second paragraph

The Examiner rejected claims 49-62 under 35 U.S.C. § 112, second paragraph, as being indefinite. In particular, the Examiner asserted that since the sequence identifiers set forth in the (unamended) claims were used to identify linear peptides in the parent application, cyclic peptides employing the same sequence identifiers did not find antecedent support in the specification.

As indicated above, Applicants have herein updated the sequence listing to provide new sequence identifiers and the appropriate description for the presently recited disulfide-linked peptides. Such new sequence identifiers are set forth in the currently amended claims. Accordingly, Applicants respectfully assert that the present claims are not indefinite, and request withdrawal of the rejections.

Rejections under 35 U.S.C. § 103(a)

The Examiner rejected claims 49-64 under 35 U.S.C. § 103(a) as being unpatentable over Keates *et al.* (Biochem. J. (1997) 324:295-303) ("Keates") in view of Wickstrom *et al.* (Biochem J. (1998) 334:685-693) ("Wickstrom"). In particular, the Examiner stated that Keates discloses the C-terminal fragment of the mucin MUCB, which includes the peptide CHFYAVC at amino acids 188-194, a sequence which corresponded to SEQ ID NO:2 of the (unamended) claims.

The Examiner acknowledged that Keates did not specifically disclose the peptide as claimed. The Examiner asserted, however, that Wickstrom discloses that MUC5B contains cysteine rich regions starting at amino acid 176, which may be folded and stabilized by disulfide bonds. The Examiner concluded that because disulfide bonds stabilize the cysteine rich region of MUC5B and because the sequence CHFYAVC is within that region, one would expect the presence of disulfides between amino acids 188 and 194. Thus, according to the Examiner, because the Applicants had allegedly admitted that the polypeptides as previously claimed in the parent case did not relate to independent and distinct inventions, the claimed polypeptides of the present case were obvious. The Examiner went on to state that according to the Decision on Petition, the claims would be rendered obvious even if the claims were limited in scope so as to exclude the first, second, or third polypeptides, and that "even if Applicants have limited the polypeptides to the cyclic peptides, the admission in the petition renders obvious the claimed peptides."

Applicants respectfully disagree. Proper analysis under § 103 requires consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition, and (2) whether the prior art would also have revealed that in so making, those of ordinary skill would have had a reasonable expectation of success. In re Vaeck, 947F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Neither of the cited references, either alone or in combination, teach or suggest the presently claimed MR imaging agents.

As indicated previously, the presently amended claims recite MR imaging agents. The MR imaging agents include a polypeptide comprising a disulfide-linked peptide having an amino acid sequence as set forth in the claims. Applicants respectfully point out that the amended and new claims set forth new sequence identifiers for the disulfide-linked peptides recited therein, with the appropriate description in the updated sequence listing. The recited polypeptides are conjugated, optionally through a linker, to a paramagnetic metal MR chelate. Finally, the MR imaging agent is capable of binding fibrin.

As stated above, Applicants respectfully assert that none of the conclusions or alleged admissions set forth in the Restriction Requirement, the Petition, and the Decision on Petition are

applicable to the present claims. The recited disulfide-linked peptides are not identical to the various polypeptides that were at issue in the Restriction Requirement, Petition, and Decision on Petition. Applicants respectfully note that the Examiner stated in the present Office Action that the various polypeptides of the (unamended) claims were considered "identical to the various polypeptides claimed, that were at issue in the petition, in the parent application . . . because both sets of polypeptides have the same sequence identifiers" and that the previous sequence identifiers were "deemed to identify linear peptides." Since the presently amended claims have new sequence identifiers respresentative of disulfide-linked peptides, the presently recited peptides cannot now be considered to be identical to the parent case's linear peptides. Further, Applicants note that in the Interview Summary dated April 3, 2003, the (prior) Examiner stated, in response to prior counsel's question regarding allowability of cyclic peptides, that "cyclic peptides *were not part of the initial restriction*, and have not been examined (emphasis added)." This interview was conducted after the Decision on Petition was mailed and in response to the prior counsel's concerns regarding that Decision. Finally, Applicants assert that the Decision on Petition did not address in any way the effect of the Applicants' prior alleged admissions regarding the parent case's linear peptides on the obviousness of peptides having a different, disulfide-linked conformations (*e.g.*, cyclic peptides). The only statement made in the Decision on Petition regarding an extension of any alleged admissions was regarding a potential limitation of claim scope to exclude the first, second, or third polypeptides -- polypeptides which the present Examiner has indicated are deemed to be linear, and not disulfide-linked. Accordingly, Applicants respectfully assert that none of the conclusions or alleged admissions resulting from the Petition and Decision on Petition are applicable to the present claims.

Notwithstanding all of the above, the present claims are not obvious over Keates in view of Wickstrom. Keates discloses the deduced amino acid sequence of the C-terminal region of human gall bladder mucin, which includes a cysteine-rich region. As acknowledged by the Examiner, Keates does not specifically disclose the peptides as presently claimed. Moreover, and contrary to the Examiner's assertions that one would "expect" the presence of disulfide-linkages between amino acids 188 and 194 of the Keates polypeptide, Keates specifically

discloses that the cysteine-rich regions are believed to participate in the formation of *intermolecular* disulfide bonds linking mucin monomers to form dimers and higher order oligomers (emphasis added); *see* Keates at page 295, Col. 2; *see also* page 302, Col. 1 (discussing generally disulfide linked polymerization of monomers via the cysteine-rich domain). Thus Keates specifically teaches away from an expectation of specific intramolecular disulfide linkages in its disclosed polypeptide -- intramolecular disulfide linkages which are required in the presently recited peptides to occur between specific cysteine residues. Indeed, given the large number of cysteine residues in the cysteine-rich region of the Keates mucin polypeptide, one having ordinary skill in the art would not have had a reasonable expectation of success that a disulfide linkage would occur intramolecularly between particular cysteine residues, as required in the presently recited polypeptides. Keates also entirely fails to teach or suggest an MR imaging agent, particularly one that is capable of binding fibrin, where the MR imaging agent comprises a polypeptide that includes the recited specifically disulfide-linked polypeptide, and where the polypeptide is conjugated, optionally through a linker, to a paramagnetic metal chelate.

Wickstrom does not cure the deficiencies of Keates. At no point does Wickstrom teach or suggest that one having ordinary skill in the art should modify the mucin polypeptide of Keates to 1) conjugate a paramagnetic metal MR chelate to such a polypeptide, optionally through a linker, to produce an MR imaging agent that is capable of binding fibrin; or 2) to include specific intramolecular disulfide linkages in the Keates polypeptide. Wickstrom, like Keates, emphasizes the polymeric nature of mucins achieved through end-to-end cross-linking of monomers into polymers by disulfide bonds; *see* Wickstrom at page 685, Col. 1. While Wickstrom mentions that the cysteine-rich region may be stabilized and folded by disulfide bonds, Wickstrom does not disclose that such disulfide bonds are intramolecular, nor does Wickstrom disclose that the disulfide bonds should be between particular cysteine residues, as required in the present claims.

Even if one having ordinary skill in the art were somehow motivated to make such modifications, he would not have a reasonable expectation of success that an MR imaging agent

capable of binding fibrin would result from such modifications. Both Wickstrom and Keates are silent as to the ability of the large, polymeric mucin polypeptides to bind fibrin. As indicated in the present specification, MR imaging agents should be prepared in such a way as not to interfere with the binding affinity or specificity of the fibrin binding moiety; *see* paragraph [0233]. Both Keates and Wickstrom provide no guidance as to MR imaging agents at all, particularly with respect to the conjugation of or location of an MR chelate on the mucin polypeptides. In addition, since the Keates and Wickstrom polypeptides are large intermolecularly cross-linked oligomers, one having ordinary skill in the art would not have had a reasonable expectation that the derivatization of such oligomers would yield a useful MR imaging agent.

Given all of the above, Applicants respectfully assert that the presently amended claims are not obvious, and request withdrawal of the rejections under 35 U.S.C. § 103(a).

CONCLUSIONS

Applicants respectfully assert that all claims are in condition for allowance, which action is hereby requested. The Examiner is invited to telephone the under-signed attorney if such would expedite prosecution.

Enclosed is a $2985 check which covers $2475 for excess claim fees and a $510 for the Petition for Extension of Time fee (three months). Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

Date: 10/2/06

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